long-term (>7 years) durability of treatment is unknown and patients should be followed up indefinitely using routine haematological tests. If loss of immunity is suspected, this should be further investigated (see examples of possible laboratory assessments below).

- Lymphocyte counts, including T-cell counts
- T-cell function as measured by T-cell proliferative capacity to mitogen challenge (TCA/PHA)
- ADA metabolites: high red blood cell dAxP levels indicate loss of ADA enzyme activity and failure of gene therapy

If loss of efficacy or inadequate efficacy of the immunological manifestations of ADA-SCID is suspected, patients can still be considered for treatment with enzyme replacement therapy (ERT) or bone marrrow transplant.

Pregnancy

Strimvelis® is not intended to correct the ADA gene defect in patient gametes (e.g. ovum, sperm), as with conventional HSCT. The effect of Strimvelis® on pregnancy is not known. Family planning is recommended for patients post-treatment with Strimvelis® at an age appropriate time during follow-up or as desired by the patient or parents/legal guardians. Use this with the Summary of Product Characteristics (SmPC) and Product Consent Form during consultations.

Contact details for reporting all suspected adverse reactions for Strimvelis®

Adverse events should be reported. For Ireland, adverse events should be reported directly to the HPRA; Freepost, Pharmacovigilance Section, Health Products Regulatory Authority, Earlsfort Terrace, Dublin 2, Tel: +353 1 676 4971, medsafety@hpra.ie. Adverse events should also be reported to GlaxoSmithKline on 1800 244 255.

IE/SVE/0004/17(1) November 2017

Important risk minimisation information for healthcare professionals who provide long-term follow-up of ADA-SCID patients post-treatment with STRIMVELIS® ▼ (autologous CD34+ cells transduced to express ADA)

New medicines and vaccines that are under additional monitoring have an inverted black triangle symbol (▼) displayed in their package leaflet and Summary of Product Characteristics, together with a short sentence explaining what the triangle means – it does not mean that the medicine is unsafe. You should report all suspected adverse drug reactions for these products – contact details are at the end of the leaflet.

When reporting possible adverse reactions please include the individual patient lot number which can be found within the patient alert card

The information contained in this leaflet is essential to ensure effective follow-up of ADA-SCID patients who have received gene therapy with Strimvelis®, and appropriate monitoring and management of selected important risks associated with its use. Therefore it is advised that you read this leaflet carefully before prescribing the product and subsequently following up patients.

Gene therapy for ADA-SCID and malignancy risk (e.g. leukaemia)

In order to make Strimvelis®, a modified retrovirus is used to insert a functional copy of the *ADA* gene into patient bone marrow cells. The process of inserting a new piece of DNA into a cell is effectively a mutation which may create a risk of leukaemia. No leukaemia has occurred in ADA-SCID patients treated with Strimvelis®, but it is possible that it could occur in the future. It is therefore important to monitor Strimvelis® treated patients for the signs and symptoms of leukaemia.

Monitoring

Parents, carers and when old enough, treated patients, should be advised about monitoring for symptoms and signs of leukaemia (e.g. breathlessness, clinical pallor, fevers, night sweats, swollen lymph nodes, easy bleeding/petechiae, frequent infections, fatigue), and should contact their doctor immediately if they develop symptoms of blood dyscrasia.
Annual monitoring as described below is recommended:

Complete blood count with red blood cell indices, white blood cell count differential, platelet count, and a routine biochemistry screen. These can be followed by a more detailed analysis if indicated, e.g. blood smear/film or cytogenetic testing.

If symptoms, signs or laboratory findings suggest leukaemia, the patient or parent should seek medical attention and report the finding immediately using the details at the end of this leaflet.

Follow-up

In order to investigate whether Strimvelis® is causing leukaemia, specialist laboratory assays are available if deemed appropriate in your work-up:

- Replication competent retrovirus – RCR
- Retroviral insertion site – RIS

A registry has been set up to follow Strimvelis® patients. It is proposed to include every patient treated with Strimvelis in this register. When you report actual or suspected leukaemia using the details above the registry administrators will contact you and tell you how to have the tests done and, if necessary, can help with interpretation of the results.

Autoimmunity

Autoimmunity is associated with the underlying immune deficiency in ADA-SCID and may be observed during immune reconstitution after gene therapy. Autoimmune reactions were reported after gene therapy, mainly between three months to three years after Strimvelis®.

Monitoring

Regular monitoring for clinical autoimmunity (possibly including tests for auto-antibodies) is routine after haematopoietic stem cell transplant (HSCT) and similar monitoring for patients is recommended post treatment with Strimvelis®.

If symptoms or laboratory findings suggest autoimmunity, the patient or parent should seek medical attention and report the finding immediately using the details at the end of this leaflet.

Unsuccessful response to gene therapy

Strimvelis® can be curative for the immune manifestations of ADA-SCID. It is not proven, nor likely to be effective for non-immunological aspects of the disease, although patients can still be considered to have had a successful response to gene therapy.

Patients should be monitored for both immunological (e.g. severe or opportunistic infections) and non-immunological manifestations (e.g. hepatic steatosis, central nervous system (CNS) manifestations, hearing impairment, neurobehavioural events) of disease. In addition, the